REMARKS

The following remarks are responsive to the Final Office Action dated April 26, 2010. Claims 1-20 are currently pending in this application and are subject to examination.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-20 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent Application Pub. No. 20030153610 (Straub et al.) in view of U.S. Patent No. 6,074,670 (Stamm et al.). Applicants respectfully traverse this rejection.

The Invention

Claims 1-20 concern a novel pharmaceutical formulation of an active compound (I) that is 5-chloro-*N*-({5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide, also known as rivaroxaban. Applicants found surprisingly that preparing granules comprising rivaroxaban in hydrophilized form by moist granulation leads to a significant increase in bioavailability. Page 2, lines 5-9.

Stamm et al. and the Obviousness Rejection

The Patent Office identified Straub et al. as teaching rivaroxaban and its use, and found that a person of ordinary skill in the art would substitute rivaroxaban for the fenofibrate taught in Stamm et al. and be motivated to prepare the formulation found in Stamm et al. with rivaroxaban and have an expectation of success. Applicants respectfully disagree.

Stamm et al. discloses compositions of fenofibrate. Stamm et al. teaches that because fenofibrate has poor hydrosolubility, it is poorly absorbed in the digestive tract and consequently its bioavailability is incomplete, irregular, and often varies from one person to another. Col. 1, lines 26-29. Stamm et al. teaches that to improve fenofibrate bioavailability, "it would be useful to increase its dissolution so that it could attain a level close to 100%." Col. 1, lines 30-33.

In Figure 1, Stamm et al. compares the dissolution curve of a prior art fenofibrate composition, Lipanthyl® 200M, and a composition according to Stamm et al. The Lipanthyl® 200M dissolution curve is shown as the bottom line in which dissolution starts slowly and continues slowly. In contrast, the tablet prepared by the asserted inventive method in Stamm et al. yielded the top dissolution curve in Figure 1, which has a faster initial dissolution rate

followed by a flattening of the dissolution curve once high level (about 83.8%) dissolution was obtained.

Because Rivaroxaban Has a Different Dissolution Profile than the Stamm et al. Drug, the Skilled Person Would Have No Suggestion to Modify Stamm et al. and No Expectation of Success.

Rejection of a claim for obviousness requires that one of ordinary skill in the art be motivated to make the modification to the prior art identified by the Patent Office and have a reasonable expectation of success with making the modification. "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). The Supreme Court has explained that the Federal Circuit's "teaching, suggestion or motivation" test provides helpful insight into the obviousness question as long as it is not applied rigidly. *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 127 S. Ct. 1727, 1741, 167 L. Ed. 2d 705 (2007).

Here, the Patent Office found that rivaroxaban was poorly water soluble as is fenofibrate. Because the formulation and process in Stamm et al. were reported to greatly enhance fenofibrate's dissolution profile and bioavailability, the Patent Office concluded that the ordinary skilled person would be motivated to formulate rivaroxaban using the Stamm et al. formulation and process with a reasonable expectation of success.

However, this argument fails because rivaroxaban does not show the poor dissolution properties that Stamm et al. describes for fenofibrate. Direct tabletting is a first choice for pharmaceutical formulations because it is very easy and relatively inexpensive when compared to other methods. When the dissolution data for directly tabletted rivaroxaban (not the inventive, hydrophilized form) as reported in the specification at Table 1 (p. 10) is placed into Figure 1 from Stamm et al., the dissolution curve for rivaroxaban is good. It resembles the improved dissolution profile that Stamm et al. obtains only after using their allegedly inventive process. Attached is a copy of Figure 1 from Stamm et al. with the data of direct tabletting from Applicants' specification added. Therefore, because direct tabletting already achieves good dissolution, the person of ordinary skill would not be motivated to modify the directly tabletted rivaroxaban to use the more complicated and more expensive fluidized bed granulation in Stamm et al.

Furthermore, the person of ordinary skill would not have a reasonable expectation of success with substituting rivaroxaban into the Stamm et al. fluidized bed granulation process. Stamm et al. teaches that its fluidized bed granulation process is used "in order to arrive at an improved dissolution profile and, thus, at elevated bioavailability." Col. 5, lines 40-43. Improved bioavailability is the endpoint that is of interest for pharmaceutical formulations. Dissolution is only a step contributing to that endpoint.

In contrast to fenofibrate, rivaroxaban when directly tabletted already showed a good dissolution profile. Therefore, the person of ordinary skill would not have had a reasonable expectation of success that by formulating rivaroxaban using the Stamm et al. process there would be improved bioavailability. Stamm et al. teaches that fenofibrate bioavailability is improved ***because the dissolution profile is substantially improved***. Where there is no room for substantial improvement in the dissolution profile, the person of ordinary skill would not expect improved bioavailability.

Yet surprisingly Applicants found that in spite of slower disintegration of the hydrophilized rivaroxaban composition as compared to the directly tabletted rivaroxaban composition, and in spite of very similar in vitro release rates, the hydrophilized composition has marked advantages in absorption and thus a bioavailability increase of about 35 %. Page 11, lines 3-5.

In sum, there is no motivation to modify Stamm et al. to replace fenofibrate with rivaroxaban and no reasonable expectation of success if the modification were made. For these reasons, Applicants respectfully reconsideration and withdrawal of the obviousness rejection of claims 1-20.

Because Stamm et al. is Narrowly Focused on Fenofibrate, Substitution with Rivaroxaban was not Suggested or Taught as Likely to Succeed.

A reference must be considered in its entirety for everything it teaches. It is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the reference fairly suggests to one of ordinary skill in the art. *In re Wesslau,* 353 F.2d 238, 241 (CCPA 1965).

Stamm et al. when read as a whole is all about fenofibrate. For example, the title begins "Fenofibrate Pharmaceutical Composition...." The Background of the Invention focuses on fenofibrate and its bioavailability and prior formulations. The specification concludes from this "[t]here is a need to improve fenofibrate bioavailability" and that "Applicant has found that, surprisingly, it is possible to resolve this problem by a new method...." Col. 2, lines 4-16. The Summary of the Invention states that "the present invention provides an immediate-release ***fenofibrate*** composition" and also the invention provides a method in which the first step is "preparing a ***fenofibrate*** suspension." Col. 3, lines 11-12 and 32-34, emphasis added. The examples all are directed to fenofibrate. The ordinary skilled person reads Stamm et al. as directed to fenofibrate compositions and would not find in the reference a suggestion to substitute another drug for fenofibrate, or a teaching that by substituting another drug for fenofibrate the same desirable results would be obtained.

In the Final Office Action, the Patent Office rejected this interpretation of Stamm et al. and instead insisted that the reference "is directed generally to active ingredients of poor aqueous solubility." Final Office Action, p. 7. To support this untenable position, the Patent Office cited to the very beginning of the application, in which the patentees merely introduced the subject matter of the patent by first describing it as relating to pharmaceutical preparations and then focusing in on fibrates, before identifying fenofibrate in the third paragraph. The remaining document addresses fenofibrate. The Patent Office also cites to usage of the term "the active ingredient" in Stamm et al. as evidence that the reference is directed to other active ingredients than fenofibrate. Yet on reading Stamm et al. as a whole one clearly sees that "the active ingredient" is a synonym for fenofibrate and is not defined or used in a manner to imply that "the active ingredient" is something other than fenofibrate.

For these reasons, Applicants respectfully request that the Patent Office reconsider its interpretation of Stamm et al. as suggesting substitution of fenofibrate with other poorly water soluble drugs, and remove the obviousness rejection.

CONCLUSION

For these reasons, allowance of the claims is respectfully requested. Alternatively, if any issues remain, the Examiner is urged to call the undersigned attorney to resolve them.

Submitted herewith is an authorization to charge the fees required for filing an RCE to the undersigned's credit card. No further fees are believed due with the filing of this paper. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 11987- 00043-US from which the undersigned is authorized to draw.

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Respectfully submitted,

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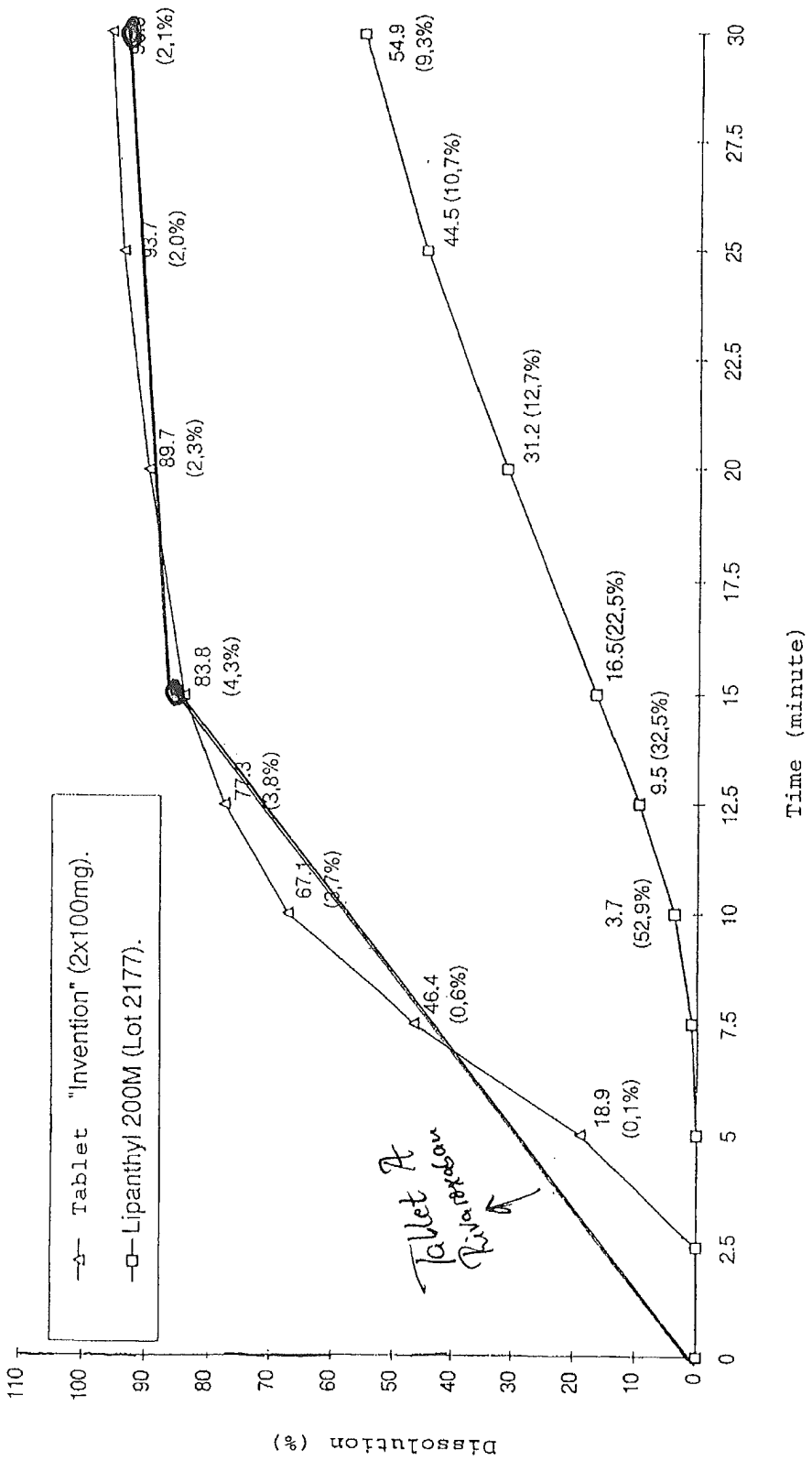
Tablet "Invention" (2x100mg).
Lipanthyl 200M (Lot 2177).
Dissolution (%)
Time (minute)
110
100
90
80
70
60
50
40
30
20
10
0
0
2.5
5
7.5
10
12.5
15
17.5
20
22.5
25
27.5
30
(2,1%)
(2,0%)
89.7
(2,3%)
83.8
(4,3%)
(3,8%)
(2,7%)
46.4
(0,6%)
18.9
(0,1%)
3.7
(52,9%)
9.5 (32,5%)
16.5(22,5%)
31.2 (12,7%)
44.5 (10,7%)
54.9
(9,3%)
Tablet A
Fenofibrate

FIG 1